Bandolier 85

What do we think?
What do we know?
What can we prove?

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One of the most important papers we are likely to read this year was published in January. It concerned the completeness of reporting of adverse events, and tells us that reporting is poor. Anyone skilled at the art of reading papers probably knew this already, but, together with other work in adverse event reporting, it sets us down a new road. The destination is better information on the benefit and harm from treatment to enable professionals and their patients to make truly informed judgements.

Informing our decisions

Both ***Bandolier*** and ***ImpAct*** rely on good feedback from readers to inform on the topics we write about. Sometimes that comes from meeting readers at meetings, and getting information directly from them. Sometimes they volunteer it by email, fax or letter. For instance, this month ***Bandolier*** has an update on glucosamine triggered by many requests.

But from time to time it is necessary to be more formal. So on the back page is a simple form that can be copied and faxed or posted to us. We want to know what topics you would like to see covered (and why if there's enough space). We want to know what parts of the Internet site you would like to see developed, either those we have or those we do not have. We want to know about people in the NHS who have made real progress in improving the service that we could write about in ***ImpAct***, based on being measureable, affordable and transferable. And finally there's a free text box for the things we haven't thought about.

Infrequently asked questions

In ***ImpAct*** comes some interesting stuff from the TRIP database in Gwent, where GPs can ask infrequently asked questions. Some of these infrequently asked questions were asked surprisingly frequently (like the efficacy of paracetamol and opioid combinations). Check out the ***Bandolier*** website and others to find an answer. That's the goal of reader surveys - to answer questions before you ask.

In this issue

*The views expressed in **Bandolier** are those of the authors, and are not necessarily those of the NHSE*

GLUCOSAMINE AND ARTHRITIS – AN UPDATE

As long ago as ***Bandolier*** 46 we performed a swift systematic review of glucosamine for arthritis. Our conclusion, after reviewing eight randomised trials, was that there existed a body of evidence supporting the use of glucosamine in arthritis. Since that time there have been two more systematic reviews published, and one superb three year study, all of which support the original conclusion. Now is a suitable time to update our knowledge, in part because the efficacy of glucosamine remains one of those questions asked most often by professionals and by the public.

Issues

There are a few points that need to be borne in mind when examining trials of glucosamine for arthritis. First is the problem that there is no international pharmaceutical standard for glucosamine (or at least none that we know of). Glucosamine is usually in the form of the sulphate, but this formulation will contain other salts and some water of crystallisation, the actual amount of glucosamine may vary from preparation to preparation, stability may be a problem, and glucosamine may be in combination with chondroitin.

Doses used also vary, as do the number of times a day oral tablets are taken. Usual oral doses are about 1 to 1.5 grams a day. Though oral administration is most common, it has also been given by injection into a joint, and by intramuscular or intravenous injection. There is no substantial evidence that this makes any difference.

Outcomes used in trials vary enormously, as is the norm in arthritis trials, especially older ones. This inhibits pooling of data in meaningful ways. Trials are often short, again as has been the case for older trials in arthritis.

Finally there is the control. Frequently this is placebo, but some studies compared glucosamine with an NSAID.

Despite these problems, two systematic reviews have been able to come to conclusions about the evidence.

Towheed et al, 2001 [1]

This Cochrane review was notable because the authors found a number of unpublished studies. In all they identified 16 randomised double-blind studies, with 992 patients randomised to glucosamine and 1037 randomised to placebo or NSAID. The mean age of patients was 61 years.

Twelve of the trials could be included in the review. All had quality scores of 3 or greater out of 5, indicating that substantial bias was unlikely.

A number of analyses of efficacy were undertaken, depending on outcome or comparator. The broad conclusion was that glucosamine had a clinically significant benefit compared with placebo based on standardised mean differences. In the review this was 1.4, and standardised mean differences (or effect sizes) of 0.8 or greater are defined as large.

The review also looked at adverse events. It found only 14 patients treated with glucosamine withdrew from treatment because of suspected toxicity, with only 61 reporting any adverse effects. Mean trial duration was only six weeks, so long-term safety might be an issue. Otherwise they concluded that glucosamine was safe and effective in treating osteoarthritis.

McAlindon et al, 2000 [2]

This review sought randomised trials of glucosamine and chondroitin in the treatment of osteoarthritis. In the analysis it pooled outcomes reported as the primary outcomes by authors of the original papers, and pooled pre-defined outcomes at four weeks, arguing that outcomes before that time may be spurious in osteoarthritis. It also pooled oral and intramuscular or intra-articular administration.

Using effect size, it found moderate to large efficacy for glucosamine (effect size 0.4) and chondroitin (effect size 1.0) with the outcomes used by authors of the original papers. Using their own hierarchy of outcomes at four weeks, effect sizes were modest (glucosamine 0.3, chondroitin 0.4). Large trials had smaller effect sizes than small trials.

Despite some concern over study quality, and of publication bias (probably misconceived as it used funnel plots, see ***Bandolier*** 81) that might exaggerate efficacy, it reached an overall positive conclusion about both glucosamine and chondroitin.

Long-term randomised trial [3]

A three-year study comparing glucosamine with placebo has just reported [3]. Patients aged over 50 years and with primary knee osteoarthritis were randomised to 1500 mg oral glucosamine sulphate once daily or placebo. The mean age was 66 years, and the mean duration of their osteoarthritis was eight years.

The primary outcome was the mean joint space width of the medial compartment of the tibiofemoral joint, with X-rays taken with patients standing, and using a validated measuring system using digitised images. Pain, functioning, stiffness and consumption of analgesics were also measured, and measurements were taken at baseline, and one and three years. Two hundred and twelve patients were randomised, and 71/106 on placebo completed three years and 68/106 with glucosamine.

The average joint space width was about 5.4 mm at baseline. With placebo there was a mean narrowing of 0.3 mm over three years. With glucosamine there was no narrowing. After three years, 32/106 patients (30%) on placebo had a significant joint space narrowing of more than 0.5 mm, compared with 15/106 patients (15%) with glucosamine. The relative risk of significant joint space narrowing with glucosamine was 0.5 (0.3 to 0.9), and the number of patients needed to be treated for three years to prevent one patient having significant joint space narrowing compared with placebo was 6.6 (3.8 to 25).

With placebo there was no overall change in pain or functioning. With glucosamine there was a significant improvement of 20-25%. Stiffness was not affected, and the consumption of analgesics or NSAIDs was not different. Patients used rescue medicines on average once every six days.

Adverse events were reported by 95% of patients over the three years. Most were transient and mild, not clearly related to treatment, and there were no differences between glucosamine and placebo. Adverse event withdrawals occurred in 21/106 patient on glucosamine and 18/106 on placebo (relative risk 1.2; 95% confidence interval 0.7 to 2.1).

Comment

Evidence that glucosamine (and chondroitin) is effective in osteoarthritis continues to build. We now have two top class reviews of older, short, studies that come to this conclusion, and a new randomised trial of some quality that demonstrates a clear disease-modifying effect, as well as showing improvements in pain and functioning and an absence of long-term harm. Added to this is the accumulating volume of anecdotal evidence from professionals who prescribe glucosamine with good effect, and of individual who use it and report the same good effects.

We might still argue that we are lacking a large randomised outcome study using a standardised glucosamine preparation, and independent of manufacturers. That is on the way. The National Institutes of Health in the USA is funding considerable research in the complementary therapy area, and glucosamine is close to, if not at the top of the list.

One practical point that emerges from several studies is that glucosamine takes about a month to exert its full effects. Another is that we now have some evidence that chondroitin is also effective. A third is evidence on formulation and stability is notable by its absence. There is no help, as yet, in choosing which of the many different preparations available is best (if any). The cheapest might be a good place to start. Glucosamine is not black-listed in the UK, but checking with health authority prescribing advisers regarding the status of reimbursement is advisable.

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IDENTIFYING PATIENTS LIKELY TO FALL IN HOSPITAL

Falls are dangerous for elderly people, and even if serious injury is avoided they can cause anxiety and reduce social and physical activity. A number of different things are likely to affect whether people fall, including their age, any disease they have, and any drugs they are taking. A large study from Italy [1] helps to identify patients in hospital at greater risk of falling.

Study

Data were collected prospectively on 7900 patients in 58 hospitals during an eight-month observation period. All admitted patients were enrolled, without exception. The study lasted to discharge or death. In Italy nurses must record all falls, and doctors must review the consequences of all falls and report serious falls to the hospital administrators.

For every patient a special questionnaire was filled out by a trained physician. This included all drugs used in hospital, and drugs used in the 30 days before entering hospital. Benzodiazepines particularly were recorded and characterised by their half-life (long – greater than 24 hours; short – 12 to 24 hours; very short – less than 6 hours). Cognitive status was also assessed with a validated scale. Diseases and diagnoses were recorded, together with comorbidities.

Incidence of falling was calculated as the number of patients with one or more falls divided by the total number of patients. A multivariate regression model was used to identify factors independently associated with falling.

Results

Of the 7900 patients 74% were older than 64 years and 34% older than 85 years. There were 1870 users of benzodiazepines. Falls occurred in 174 patients (2.2%). Multivariate analysis identified a number of factors independently associated with an increased risk of a fall (Table 1). The incidence of falls increased dramatically as combinations of these risk factors occurred together (Figure 1).

Table 1: Independent risk factors identified by multivariate analysis

Item	Multivariate odds ratio (95% CI)
Age >80 years	2.7 (1.5 to 4.7)
Benzodiazepine very short half life	1.9 (1.03 to 3.3)
Benzodiazepine short half life	1.8 (1.2 to 2.8)
Other psychotropic agent	2.3 (1.6 to 3.2)
Antidiabetic drug	1.5 (1.03 to 2.2)
More than 5 drugs	1.6 (1.02 to 2.6)
Three or more diseases	1.7 (1.05 to 2.8)
Cognitive impairment	1.6 (1.08 to 2.3)
Length of stay 17 days or more	2.1 (1.4 to 3.3)

Comment

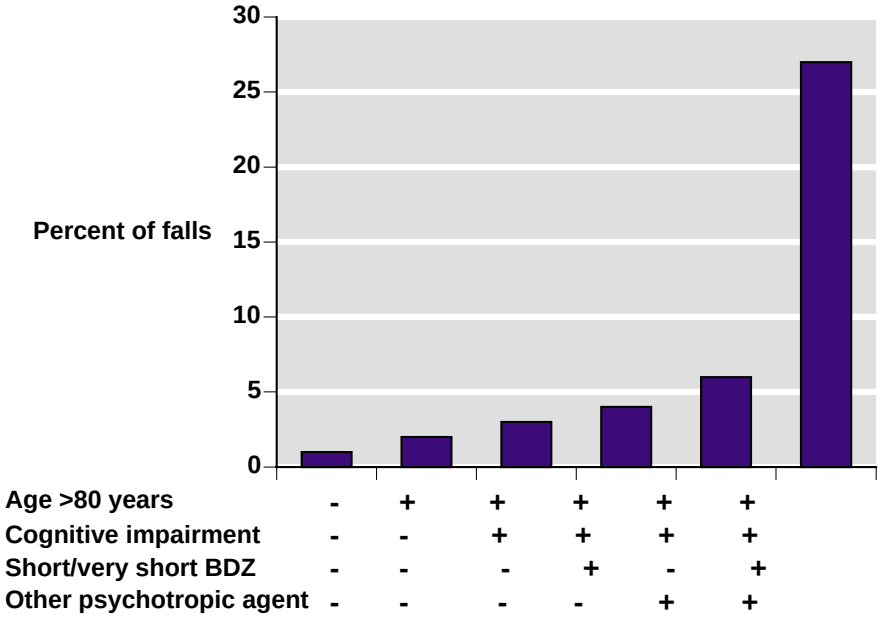
The study was large, which is good, and prospective, which is good, and took considerable trouble over data collection, which is also good. Despite this there was incomplete collection in 1250 patients.

What it does is to give us an insight into those facets of the patients, their condition, and their treatments that can contribute to an increased risk of falling. When several of the risk factors occur together, risk can be significant. If patients at increased risk can be identified, trouble can be taken to ensure their safety.

References:

1 A Passaro et al. Benzodiazepines with different half-life and falling in a hospitalized population: the GIFA study. Journal of Clinical Epidemiology 2000 53: 1222-1229.

Figure 1: How the incidence of falling increases with combinations of risk factors



OBESITY AND HEALTH

Bandolier was overcome with a sinking feeling when the newspapers in the UK highlighted a National Audit Office (NAO) report on obesity. It is a big problem (no pun intended), we are aware that obesity is associated with impaired health, and it is just about one of the most difficult topics to get to grips with. On the one hand it is just eating too much and exercising too little, but on the other it is associated with almost every aspect of our lives, from transport, to education, our jobs and our leisure.

Much too big a problem. And yet ***Bandolier's*** 10 tips for health living (***Bandolier*** 78) produced a huge response from professionals and the public, even being reproduced in a national newspaper.

So we visited the NAO Internet site (www.nao.gov.uk) and downloaded the report [1]. It is a terrific document, being of a reasonable length (74 pages), readable, informative and comprehensive. It may not have actual diet sheets or guaranteed ways to lose weight painlessly, but for those dealing with patients or making policy it comes into the must read category. It is particularly valuable because it examines the issues across all government activities, and because the case studies show how imaginatively the complicated issues about health promotion can be tackled.

Bandolier thought it worthwhile, therefore, to pick out some of the more useful items from the report, and to examine a few studies relating to obesity that have swum into our ken recently.

Background

Overweight is a body mass index (weight in kg divided by height in metres squared) of 25 to 30. A BMI between 30 and 40 is obese and above 40 is morbidly or severely obese. Someone 5 feet 6 inches tall (1.68 metres) becomes obese at 13 stone 4 pounds (84 kg) and morbidly obese at 17 stones 7 pounds (110 kg) (Note that the ***Bandolier*** healthy living website has a neat coloured chart in feet, inches, metres, lbs, kg and stones and pounds, or any combination of these)

In England 1 in 5 adults are obese, and that proportion has trebled over the last 20 years. In adults over 45 years, two-thirds are overweight or obese. Obesity is more common in women in lower socioeconomic groups, and obesity is more common in some ethnic groups.

Table 1: Relative risk of different diseases in obese versus nonobese people

	Relative risk	
Disease	**Women**	**Men**
Type 2 diabetes	12.7	5.2
Hypertension	4.2	2.6
Heart attack	3.2	1.5
Colon cancer	2.7	3
Angina	1.8	1.8
Gall bladder disease	1.8	1.8
Ovarian cancer	1.7	
Osteoarthritis	1.4	1.9
Stroke	1.3	1.3

Obesity predisposes us to higher risks of associated diseases (Table 1). There is a high human cost in diabetes, hypertension and other disorders, including cancer. There is a big cost to the NHS (Figure 1; estimated by the NAO to be £500,000,000 a year in 1998, though this may be a low estimate), and a big cost to society through lost work time and economic output (estimated by the NAO to be around £2,000,000,000 a year).

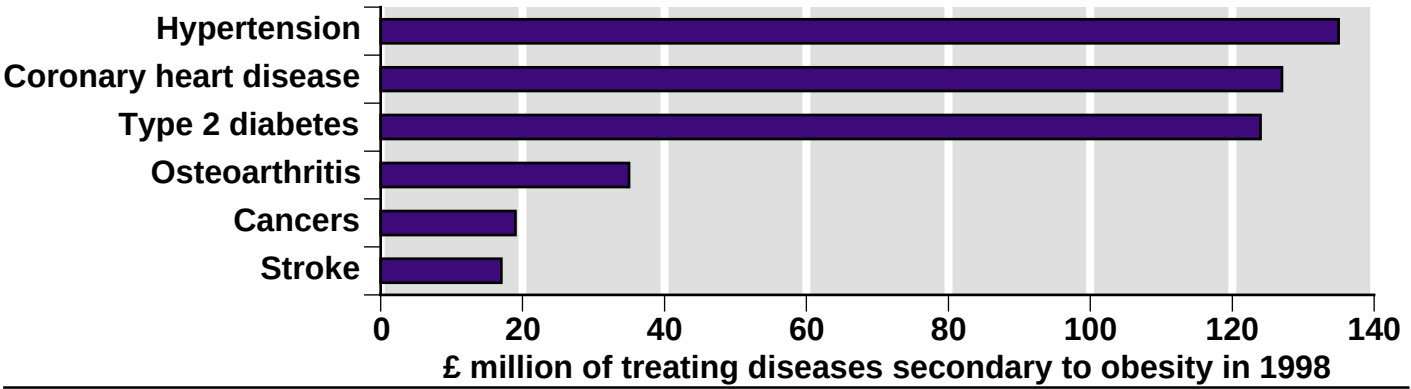
Childhood obesity and sweetened drinks

Sugar-sweetened soft drinks are consumed daily by about 70% of American adolescents. Excessive weight is now the most common paediatric medical problem in the USA. Is there any relationship between these two statements? A study on over 500 US children [2] suggests that there is.

The study was observational, involving comprehensive data collection on 548 children in Boston in October 1995 and May 1997. The data collected included the amount of sweetened and diet soft drinks consumed at baseline and at the follow up, and diet and energy intake, and BMI and triceps skinfold thickness, and activity analysis. It also involved some considerable analytical expertise to construct a number of different models involving possible confounders relating consumption of sweetened soft drinks to development of obesity.

There were 548 children in total, of whom 398 were not obese at baseline, but 37 of these 398 became obese at follow up. Sixty percent of the children reported drinking more sweetened soft drinks between baseline and follow up, and 25% were drinking one more serving a day.

Figure 1: Annual cost of obesity-related disease in England



The odds ratio of becoming obese increased by 1.6 times for each additional can or glass of sugar sweetened drink consumed every day. Consumption of diet-soda was negatively associated with obesity incidence.

Obesity and cancer

A new analysis [3] tells us more about obesity and cancer. Articles relating body weight with cancer incidence for a range of different cancers were sought and subjected to individual meta-analyses to explore the dose-response between increasing BMI and cancer risk. This information was then combined with prevalence of persons overweight (BMI 25 to 30) and obese (BMI above 30) in each of the 15 EU countries to obtain estimates of the number of cancers attributable to overweight, and the percentage of cancers attributable to overweight (for about 1995).

Information is given for each country individually, and the whole EU. The figures for the UK are given for the percentage and number of cancers in Figures 2 and 3. The total number of cancers attributable to overweight in the UK was 9,000 (it was 70,000 for the EU), and the percentage of cancers was 2.7% for men and 4.9% for women.

Low fat diets produce weight loss

A meta-analysis is highly supportive of the role of low fat ad libitum diets [4] for weight loss in the obese. The review sought studies of at least three months duration of ad libitum diets comparing low fat with normal diet, and which reported weight change as an outcome. Fifteen publications of 16 studies were found, 13 of which were randomised. The total number of patients was 1728, of whom 1074 were women. The mean BMI was 21-29, and the studies lasted between nine weeks and 12 months.

Low fat diets produced reductions in percentage of energy from fat from 3.5% to 24%, and with mean weight losses in individual trials of up to 10 kg. The overall mean weight loss associated with a low fat diet was about 2.5 kg (results for randomised studies in Figure 4). The amount of weight loss was related to the degree of fat reduction in control and intervention groups (Figure 5, randomised studies). With no reduction in dietary fat, no weight loss occurred. For every 1% reduction in dietary fat there was a weight loss of 0.4 kg.

Weight loss was least in those with body weights in the range of 60-72 kg. Weight loss increased progressively with increased initial body weight. Extrapolated to an initial weight of 88 kg and a 10% reduction in fat, the predicted weight loss would be 4.4 kg.

Comment

The explosion in overweight and obese adults and children is a real problem with major implications for the health of individuals and for organisations delivering health care. It is a worldwide problem, and it is predicted to get much worse.

Figure 2: Percent of cancers related to obesity (UK)

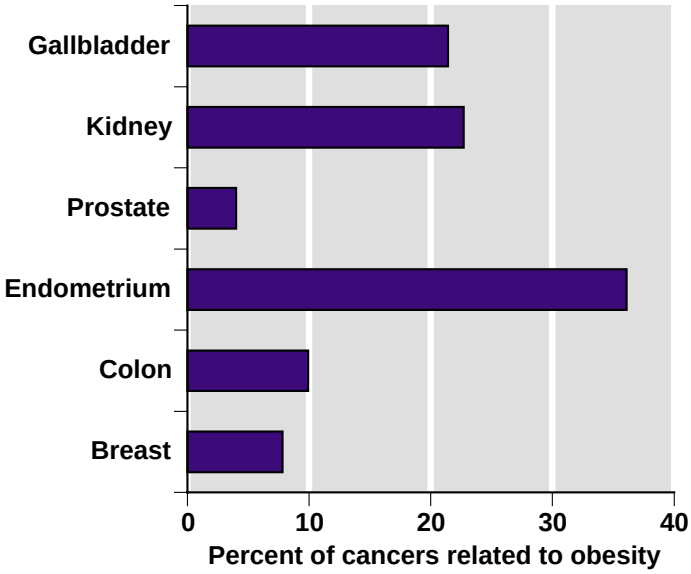


Figure 3: Number of cancers related to obesity (UK)

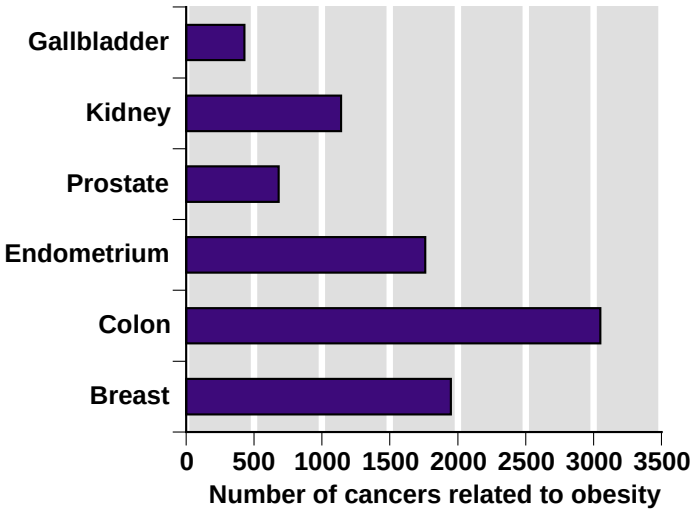


Figure 4: Weight change in ad libitum low fat versus normal diets

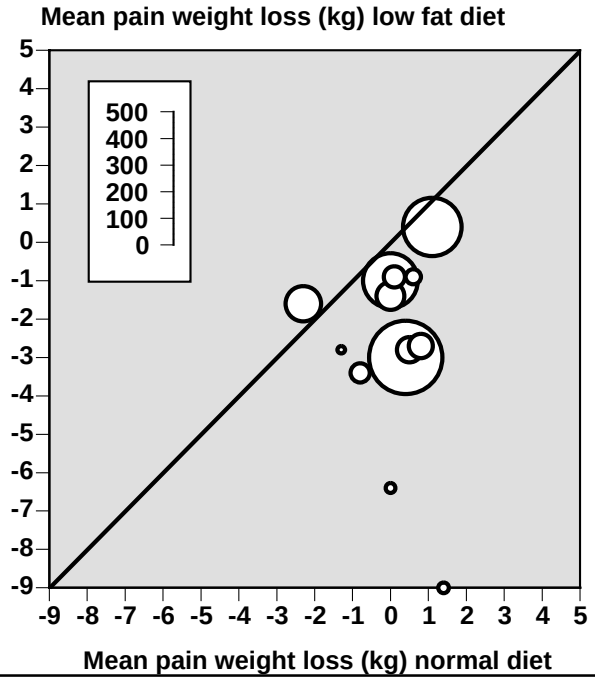
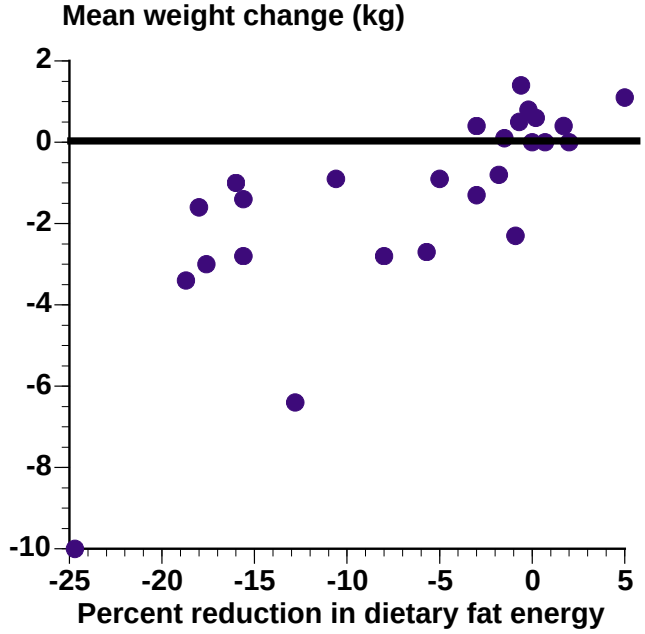


Figure 5: Relation between fat reduction and weight loss (all groups)



Put simply, we eat too much and do too little, and what we eat is often injurious of itself. Health promotion is clearly advocated, though this is a complex matter, and there are few beacons of success. ***Bandolier*** has had difficulty finding good quality evidence about successful delivery of health promotion messages, but that may be because we are looking in the wrong place. We'd love to hear of examples in the literature, or examples that could be written up for ***ImpAct***.

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Adverse events – can we trust the data?

Establishing how good a new intervention really is is relatively straightforward, but there has been a more casual attitude about measuring harm from treatments. It is appropriate that the way harm is measured and reported in randomised trials is now getting more attention [1], and now getting more attention in clinical trial design as well.

Study

The study [1] set out to examine adverse event reporting in seven medical areas. These were HIV therapy, antibiotics for acute sinusitis, thrombolysis for acute myocardial infarction, NSAIDs for rheumatoid arthritis, hypertension in the elderly, treatment of Helicobacter pylori with antibiotics and selective decontamination of the gastrointestinal tract. Trials for each topic were identified from systematic reviews and meta-analyses and comprehensive databases of randomised trials. Meta-analyses were not updated.

Reporting adverse events

Adverse event reporting was examined both qualitatively and quantitatively, based on criteria previously defined for HIV [2]:

- Information on adverse events should be given with numbers.
- The severity of adverse events should be stated, and as a minimum the frequency of severe or life-threatening events should be provided for each study arm.
- Information should be given for each specific type of severe adverse event.

Based on these criteria, two components were selected:

1 Whether the number of withdrawals and discontinuations because of adverse events were reported, and whether the number was given for each specific type of adverse event leading to withdrawal.

2 Whether the severity of the described adverse event (or abnormalities of laboratory tests) were adequately defined, partially defined, or inadequately defined.

To be adequate, a detailed description of the severity or reference to a known scale of severity needed to be given, with separate reporting of at least severe or life-threatening events, and with at least two adverse events defined in this way with numbers for each study arm.

To be partially adequate, reports combined moderate with severe or life threatening, or had separate reporting for one of many reported adverse events.

To be inadequate, reports gave the total number of severe adverse events without giving details on specific types, lumped together all grades, or gave only generic statements, or had no information at all on adverse events.

Results

There were 192 randomised trials in the analysis, 61% of which were additionally double-blind. The total number of patients was 130,000. Most of the trials were published before the 1990s, though some were published as recently as 1999. About a third were published in journals with impact factors of 7 or more, so they were by no means all published in obscure places.

The number of discontinuations per study arm was reported in 75% of trials, though the reason for the discontinuations per study arm was given in only 46% of trials (Table 1). The best clinical areas for reporting the number and reason for adverse event discontinuations were antibiotics for acute sinusitis, and arthritis.

Adequate reporting of clinical adverse events was found in 39% of trials, partially adequate reporting in 11%, and in-

Table 1: Percent of trials with different adverse event reporting outcomes

Reporting of safety	Percent of trials	Range
Discontinuations because of harm		
Number per arm given	75	30-100
Reasons per arm given	46	20-68
Clinical adverse events		
Adequate reporting	39	0-62
Partially adequate reporting	11	0-20
Inadequate reporting	50	22-100
Laboratory defined toxicity		
Adequate reporting	29	0-62
Partially adequate reporting	8	0-20
Inadequate reporting	63	25-100

Range refers to the limits found in each of seven clinical areas.

adequate reporting in 50% of trials (Table 1). The best areas for reporting clinical adverse events (adequate plus partially adequate) were thrombolysis for myocardial infarction, and arthritis.

Adequate reporting of laboratory adverse events was found in 29% of trials, partially adequate reporting in 8%, and inadequate reporting in 63% of trials (Table 1). The best areas for reporting clinical adverse events (adequate plus partially adequate) were treatments for HIV, and arthritis.

Comment

This business of adverse event reporting is both difficult and important. Importance is obvious: patients and professionals need to know the likelihood of a treatment not only being effective, but also producing harm. Harm can be common, mild, and reversible. It could be rare, major and irreversible. Individuals will view their importance differently. A flautist may view with dismay a treatment causing dry mouth, while others of us will simply drink more. A man or woman in their 30s with a family depending on them will think differently about a risk of death of 1 in 1000 than will a single person in their 70s, even if the benefit is the same. Truly one man's meat is another man's poison.

But as this report [1] shows, the chances of us being well informed even from good quality randomised trials for efficacy is slight, because of deficiencies in recording or reporting adverse events. There were some obvious results. That HIV treatments did well on laboratory-defined adverse events was not surprising, because in HIV surrogate laboratory measures are important. That arthritis trials did well on clinical adverse event reporting (and discontinuations) was not surprising because NSAIDs are known to cause gastrointestinal bleeding.

What is not surprising to those who undertake systematic reviews, and therefore read many trial reports, is that overall adverse event reporting was poor. One important lesson, though, is that one type of adverse event, that of the number of discontinuations per study arm, is the best reported, and one that should therefore feature highly in systematic reviews as a useful marker of overall toxicity of a treatment.

Further thoughts

It isn't just reporting adverse events that is important. This paper [1] and others [3] suggest improvements to the ways that adverse events can be reported in clinical trials and even suggest amendments to CONSORT [4], a set of guidelines about reporting clinical trials that was a bit light on how it treated adverse events.

But there may be even more fundamental ways in which our knowledge is deficient. For instance, the way in which adverse events are recorded can give rise to significantly different rates [3]. Which is right? Difficult to know. Then there's the problem that adverse event recording for long-term treatments can include things like chest infections and other common minor ailments that have nothing to do with treatment. Unless there is some sifting, the results merely serve to confuse. For some conditions like migraine, we measure efficacy over one day and harm over one week. Why? What relevance does this have?

One thing is certain. Despite there being significantly important lessons about harm that can be gleaned from systematic reviews of the literature [5 and 6 are examples], there is much we do not yet know. And we need it, especially if we are to inform professionals and the people they treat so that truly informed decisions can be made.

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